Synthesis of Thia-ellipticine, 5,11-Dimethylbenzothieno[2,3-g]isoquinoline (1)

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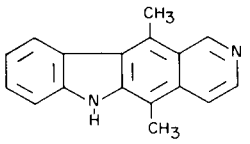
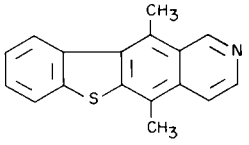
1,4-Dimethyldibenzothiophene (VII) was synthesized and was converted with butyl dichloromethyl ether to the 2-aldehyde (VIII). The structure was confirmed by an independent synthesis of the 2-ester (XI) derived from it. The 2-aldehyde (VIII) with aminoacetaldehyde diethylacetal formed the Schiff's base (IX), and Pomeranz-Fritsch cyclization with 105% superphosphoric acid then formed thia-ellipticine (II), an isostere of the antitumor alkaloid, ellipticine.

Recent interest in the antitumor properties (2) of the alkaloid ellipticine (I) has prompted the synthesis and testing of various structural analogs (3,4). Another subtle change consists in replacing the carbazole *NH* with other heteroatoms, forming isosteres of I which may have similar or even enhanced properties. This report describes the introduction of a sulfur atom at this position to give



I



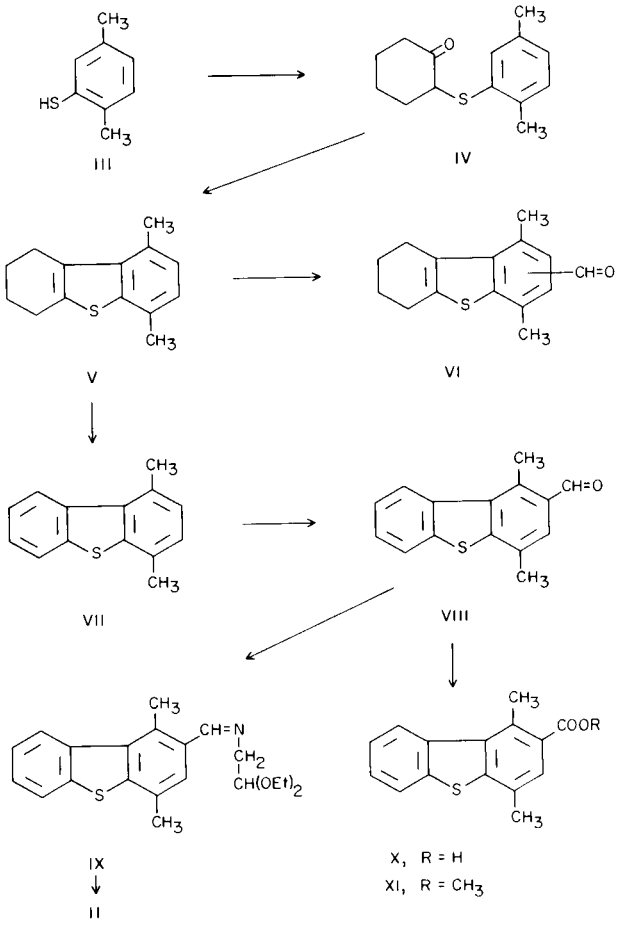
II

thia-ellipticine (II). The synthesis was from 1,4-dimethyldibenzothiophene (VII) in a three-step synthetic sequence, similar to that used for a recent synthesis (2) of ellipticine.

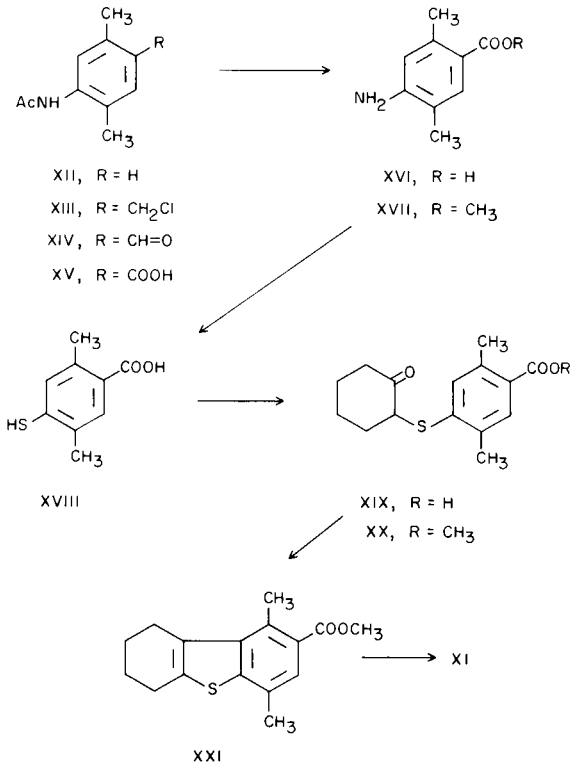
1,4-Dimethyldibenzothiophene was easily prepared from 2,5-xylenethiol (III) (5,6). Treatment of III in aqueous alkaline solution with 2-chlorocyclohexanone (7) afforded the xylylthio ketone (IV), which was cyclized with polyphosphoric acid (8,9) to 1,2,3,4-tetrahydro-6,9-dimethyldibenzothiophene (V). Catalytic dehydrogenation at 350° yielded 1,4-dimethyldibenzothiophene (VII). The 2-aldehyde (VIII) was obtained by reaction with butyl dichloromethyl ether and stannic chloride (10). Substitution of the formyl group *para* to the sulfur was expected from known substitution reactions of the parent heterocycle (11) and by analogy with 1,4-dimethylcarbazole (2) and 1,4-dimethyldibenzofuran (currently being studied in some related work). The structure of the aldehyde (VIII) was confirmed by an independent synthesis (Scheme II) of the 2-ester (XI) derived from it.

The aryl methyl groups in 1,4-dimethyldibenzothiophene (VII) showed a separation of about 0.3 ppm in the nmr spectrum. The more deshielded (δ 2.78) of the two

SCHEME I



SCHEME II



could be designated the 1-methyl group, by observing that it was even further deshielded (δ 2.99) when the aldehyde was substituted in the adjacent 2-position in VIII. Resonance of the other methyl group remained virtually unchanged (δ 2.48 vs 2.45) in going from VII to VIII and must be the non-adjacent 4-methyl group. The deshielding effect of an aryl aldehyde on an adjacent aryl methyl group was recently noted (2) with the carbazole analogs of VII and VIII.

The nmr spectrum of the crude aldehyde (VIII) showed a minor impurity (10% maximum) which may have been the isomeric 3-aldehyde, but which was removed by recrystallization. In contrast to the high isomeric purity of VIII, the product from the tetrahydrodibenzothiophene (V) and butyl dichloromethyl ether-stannic chloride was a mixture of aldehydes (VI) that could not be separated by recrystallization. It appeared that the 3-isomer of VI (substitution *meta* to sulfur) predominated over the 2-isomer in a ratio of 70/30. It has been reported (12) that *meta* substitution occurs with tetrahydrodibenzothiophenes. The minor component of VI was identified as the 2-isomer by the relatively wide spacing, in the nmr spectrum, of the two methyl singlets (δ 2.93 and 2.43), which resembled the methyl singlets of VIII (and of the esters XXI and XI). The wide spacing was again attributed to downfield shift of the 1-methyl group (from δ 2.67 to 2.93), in going from V to VI; resonance of the 4-methyl group was unchanged at δ 2.43. These methyl resonances seemed to be little affected by whether the unsubstituted A-ring of the heterocycle was aromatized or at the tetrahydro level as evidenced by the small changes in going from V to VII. Unlike the widely spaced methyl singlets of the 2-isomer of VI, those of the major 3-aldehyde were nearly coincident (δ 2.73 and 2.67) in the nmr spectrum owing to downfield shift of the 4-methyl (from δ 2.43 in V to 2.73), while the 1-methyl group was now unchanged (at δ 2.67) from that in V.

The aldehyde (VIII) was allowed to react with aminoacetaldehyde diethyl acetal to form the Schiff's base (IX). Cyclization occurred with hot "105% superphosphoric acid" (13) to form thia-ellipticine II. There was also polymer formation and hydrolysis of IX to the aldehyde precursor VIII, and consequently the yield of II was only 35%. A cyclization like this was the final step in the best synthesis of ellipticine recently reported (2); the yield of ellipticine could not be improved above 44%, presumably for similar reasons.

For structure confirmation, the aldehyde (VIII) was oxidized to the carboxylic acid (X) and esterified. The methyl ester (XI) was independently synthesized (Scheme II) starting from 2',5'-acetoxylidide (XII). Chloromethylation of XII and oxidation of the resultant benzyl chloride (XIII) with sodium 2-nitropropanenitronate afforded the *p*-acetamido aldehyde (XIV) in high yield; it could not be obtained directly from XII with butyl dichloromethyl ether-stannic chloride. Treatment with silver oxide oxidized XIV to the acetamido acid (XV); with prolonged heating, 4-amino-2,5-dimethylbenzoic acid (XVI) was obtained directly from the aldehyde (XIV). The 4-mercapto acid (XVIII) was obtained from the diazonium salt of XVI by treatment with sodium polysulfide and reduction of the intermediate disulfide of XVIII with zinc and acetic acid. The *para* relationship of functional groups on the benzene ring in this series was clearly seen in the nmr spectra of the acetamido aldehyde (XIV), the ester (XVII) (from the amino acid intermediate XVI), the mercapto acid (XVIII), and the (ketothio)ester (XX). For each compound, the two aromatic protons (also *para*) appeared in the nmr as two slightly broadened singlets ($J \leqslant 1$ Hz), diagnostic for the *para* relationship (14). The alternative, *ortho* substitution, would give two *ortho* protons with a distinctive AB quartet (J = 6-10 Hz) (14,15). The mercapto acid (XVIII) in alkaline solution reacted with 2-chlorocyclohexanone, and the product (XIX) was esterified and cyclized to form the tetrahydro compound (XXI), purified chromatographically. The dehydrogenation product (XI), also purified chromatographically, was identical to the ester (XI) from Scheme I.

In all the nmr spectra studied for dibenzothiophene derivatives, the noticeable deshielding of protons H-9 and H-6 below the normal resonance of aromatic protons was characteristic for the unsubstituted dibenzothiophene ring, in accord with a recent report (16). For the benzothienoisoquinoline (II), this effect for the corresponding protons (H-10 and H-7) was less striking, but the pyridine ring was readily characterized by the strong deshielding of the protons adjacent to the pyrido N (H-1 and H-3) as in ellipticine (2).

Synthetic studies are in progress on related alkaloids with the sulfur in a higher oxidation state, and with other heteroatoms in place of the carbazole *NH*.

EXPERIMENTAL

Methods.

Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Nmr spectra were determined with a Varian A-60 spectrometer; 2% tetramethylsilane was the internal standard (δ 0.00). Accuracy is ± 0.05 ppm for chemical shifts. Signals are described as singlet (s), doublet (d), quartet (q) or multiplet (m). Solutions for preparative thin-layer chromatography were applied to plates with the Rodder streaker, Rodder Instrument Co., Los Altos, California. In processing, solutions were dried with magnesium sulfate, which was removed by filtration; solutions were concentrated *in vacuo*.

2-(2,5-Xylylthio)cyclohexanone (IV).

A solution of 35 g. (0.25 mole) of 2,5-xylenethiol (III) (5,6) and 14.5 g. (0.26 mole) of powdered potassium hydroxide in 40 ml. of water, stirred under nitrogen, was cooled to 0° (in one experiment the potassium salt precipitated), and treated in portions with 33.6 g. (0.25 mole) of 2-chlorocyclohexanone during a period of 20 minutes. A white precipitate formed and 100 ml. of water was added to facilitate stirring. After 1 hour, the mixture was heated at 95-100° for 2 hours; a *p*H of 10 was maintained by addition of more hydroxide. The product, a supernatant oil, was extracted with two 200-ml. portions of benzene. The combined benzene extract was washed with two 200-ml. portions of water, dried, and concentrated to a syrup (53 g., 91%) which was distilled. After collected of a forerun (5 g.), a fraction of 40 g. (68%) was obtained, b.p. 150-152° (0.25 mm), which crystallized on standing, m.p. 44-48°; ir (Nujol) μ 5.86 (C=O); nmr (deuteriochloroform) δ 7.25-6.75 m (3 aryl H's), 3.85-3.58 (rough triplet of doublets, CO–CH–S), 3.15-2.6 m, (CH_2CO–), 2.33 s and 2.25 s (aryl CH_3's), 2.4-1.5 m (three CH_2's). The multiplet of aryl protons could be interpreted as 7.18 s (broad, H-6, $J_{4,6}$ = 2 Hz), 7.02 d (H-3, $J_{3,4}$ = 8 Hz, $J_{3,6}$ <1Hz), 6.88 q (H-4, $J_{3,4}$ 8 Hz, $J_{4,6}$ = 2Hz).

Anal. Calcd. for $C_{14}H_{18}OS$: C, 71.7; H, 7.71; S, 13.7. Found: C, 71.8; H, 7.65; S, 13.4.

1,2,3,4-Tetrahydro-6,9-dimethyldibenzothiophene (V).

The ketone (IV) (4.3 g., 18 mmoles) was thoroughly mixed with 60 g. of polyphosphoric acid (theoretical phosphorus pentoxide content, 82-84%) by stirring, the mixture was immersed in an oil bath at 75-80° and stirred for 3 hours, then was cooled and poured slowly with stirring into 400 ml. of ice and water. The product separated as an oil, and after several hours was extracted with two 100-ml. portions of dichloromethane. The combined extract was washed with 100 ml. of saturated sodium bicarbonate, with 100 ml. of water, and was dried and concentrated to a residual oil, 3.5 g. (88%). Distillation at 154-156° (0.40 mm.) afforded 2.4 g. (60%) which crystallized on standing, m.p. 33-35°; nmr (deuteriochloroform) δ 6.88 s (H-7 and H-8), 3.2-2.6 m (benzylic CH_2's at C.1 and C.4), 2.67 s (9-CH_3), 2.43 s (6-CH_3), 2.0-1.7 m (CH_2's at C.2 and C.3).

Anal. Calcd. for $C_{14}H_{16}S$: C, 77.7; H, 7.43; S, 14.8. Found: C, 77.4; H, 7.37; S, 15.0.

1,4-Dimethyldibenzothiophene (VII).

A mixture of 0.90 g. (4.1 mmoles) of tetrahydrocompound V and 225 mg. of 30% palladium-carbon was refluxed at 340-350° for 4.5 hours. To the cooled mixture, 40 ml. of dichloromethane was added and the catalyst was removed by filtration. Concentration of the filtrate afforded 0.75 g. (85%) of clear oil, identical according to ir and nmr spectra to an analytical sample obtained by distillation of a larger sample at 137-139° (0.07 mm.); nmr (deuteriochloroform) δ 8.37-8.16 m (H-9), 7.88-7.63 m (H-6), 7.5-7.15 (H-7 and H-8), 7.03 s (H-2 and H-3); 2.78 s (1-CH_3), 2.48 s (4-CH_3).

Anal. Calcd. for $C_{14}H_{12}S$: C, 79.2; H, 5.72; S, 15.1. Found: C, 79.4; H, 5.78; S, 14.9.

1,4-Dimethyl-2-dibenzothiophenecarboxaldehyde (VIII).

Method A.

A stirred solution at 0-3° of 1.06 g. (5.00 moles) of the dibenzothiophene (VII) in 15 ml. of dichloromethane was treated with 0.87 ml. (4.10 mmoles) of anhydrous stannic chloride. To the cold, stirred solution was added 1.05 ml. (7.53 mmoles) of butyl dichloromethyl ether (10). The resultant dark mixture was clarified by adding 6 ml. more dichloromethane and was stirred at 0-3° for 50 minutes, then was poured rapidly with vigorous stirring into 80 ml. of ice and water. More dichloromethane (25 ml.) was added, the mixture was stirred, and the clear organic layer was separated. The acidic aqueous layer was extracted with 35 ml. of dichloromethane. The combined organic solutions were washed with 75 ml. of saturated sodium bicarbonate, with two 75-ml. portions of water, were dried, and concentrated to form 1.2 g. (100%) of white solid, m.p. 92-103°; integration of extraneous singlets in the nmr spectrum at 10.2 δ(possibly –CH=O of the 3-aldehyde) and 2.7 δ (possibly both methyls of the 3-aldehyde, plus a non-aromatic impurity) suggested the presence of up to 10% of the isomeric 3-aldehyde, which was removed by recrystallization from 11 ml. of 2-propanol, giving 0.88 g., m.p. 101-106°. A second recrystallization from 13 ml. of cyclohexane yielded 0.66 g. (55%), m.p. 104-107°; ir (Nujol) μ 3.68 (aldehyde CH), 5.93 (C=O); nmr (deuteriochloroform) δ 10.37 s (–CH=O), 8.37-8.15 m (aryl H-9), 7.90-7.70 m (aryl H-6), 7.58-7.28 m (3 aryl H's), 2.99 s (1-CH_3), 2.45 s (4-CH_3). An analytical sample, m.p. 104-106°, from another run was otherwise identical.

Anal. Calcd. for $C_{15}H_{12}OS$: C, 75.0; H, 5.02; S, 13.3. Found: C, 74.9; H, 4.80; S, 13.3

Method B.

Regeneration from the iminoacetal (IX).

A suspension of 5.35 g. (15.0 mmoles) of IX in 100 ml. of 3 *M* hydrochloric acid was refluxed for 3.5 hours and cooled. The crude product was collected on a filter, washed with water, and dried (3.5 g., m.p. 105-110°). Recrystallization afforded 3.0 g. (85%), m.p. 109-110°, identical in the infrared to the aldehyde from Method A.

1,4-Dimethyl-2-(2,2-diethoxyethylamino)methyldibenzothiophene (IX).

A mixture of 105 mg. (0.436 mmole) of 2-aldehyde VIII and 0.09 ml. of aminoacetaldehyde diethyl acetal was heated at 95-100° for 2.5 hours, then benzene (10 ml.) was added and distilled off to remove the water formed. This was repeated twice, leaving a syrup which crystallized on standing (124 mg.). Recrystallization from hexane afforded 100 mg. (64%), m.p. 86.5-88°. A sample melting at 87-89° was analyzed; ir (Nujol) μ 6.10 (C=N), 8.9 and 9.3-9.5 (acetal C–O–C).

Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.9; H, 7.10; N, 3.95. Found: 71.0; H, 6.96; N, 3.87.

5,11-Dimethylbenzothieno[2,3-*g*]isoquinoline (II).

To 145 g. of freshly opened 105% superphosphoric acid (13,17), stirred and heated at 130°, was added in portions, over 4 minutes so as to prevent lumping, 6.67 g. (18.7 mmoles) of the Schiff's base IX. The dark homogeneous mixture was stirred at 130° for 30 minutes, then poured with stirring into 200 ml. of ice and water. The hydrolysate was stored overnight, and the solid (phosphate salt of II) was collected on a filter, washed with 25 ml. of water, and triturated with three 50-ml. portions of dichloromethane to remove any regenerated aldehyde VIII or other non-phosphate. The solid was then suspended in 70 ml. of 10% sodium hydroxide and heated for 30 minutes on the steam bath, while it turned gummy, then solid again; it was pulverized, stirred in the alkaline suspension overnight, collected on a filter, and washed with water. The crude free base (II) weighed 4.23 g. (86% yield, 60% purity estimated from the uv extinctions). The product was extracted from polymeric material by trituration with four 50-ml. portions of hot methanol; the combined methanol filtrates were concentrated to a residual solid (1.94 g., 92% purity by uv), m.p. 143-147.5°. An additional 0.23 g., m.p. 142-151°, was recovered from the methanol-insoluble solid by trituration with two 20-ml. portions of hot 3 *M* acetic acid, filtration, basification of this filtrate, and extraction of the precipitate with dichloromethane. The combined product (2.17 g.) was recrystallized from 25 ml. of hot methanol; the solution was decanted from small amounts of dark oil which separated, and refrigeration overnight afforded 1.72 g. (35%) m.p. 146-149° (dried at 80° *in vacuo*). The compound showed great affinity for small amounts of solvent. A sample recrystallized from dichloromethane-carbon tetrachloride, even after drying at 140° *in vacuo* for 48 hours, m.p. 147-151°, showed 1% Cl. For another sample recrystallized from methanol, drying at 80° *in vacuo* was insufficient to remove the last few percent of solvent, but after 48 hours at 140° a solvent-free sample was obtained, m.p. 152.5-153.5°; uv (ethanol) λ max mμ 228 (ϵ, 23,700), 242 (ϵ, 26,100), 249 sh, 257 (ϵ, 28,100), 278 (ϵ, 71,700), 285 (ϵ, 72,500); ir (Nujol) μ 6.28, 12.37, 13.05-13.1, 13.64 (strong bands, unassigned); nmr (deuteriochloroform) δ 9.52 s (H-1), 8.47 d (H-3, $J_{3,4}$ = 6 Hz), 8.08-7.92 m (H-10), 7.78-7.25 m (4 aryl H's), 2.79 s (11-CH_3), 242 s (5-CH_3).

Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.5; H, 4.97; N, 5.33; S, 12.2. Found: C, 77.4; H, 5.27; N, 5.33; S, 12.0.

1,4-Dimethyl-2-dibenzothiophenecarboxylic Acid (X).

A refluxing solution of 241 mg. (1.00 mmole) of the 2-aldehyde (VIII) in 15 ml. of acetone was treated with a solution, added in portions during 0.5 hour, of 350 mg. (2.20 mmoles) of potassium permanganate in 40 ml. of acetone and 10 ml. of water. The mixture was refluxed for 5 hours, stored overnight, and filtered to remove manganese dioxide. The filtrate was concentrated, and the residual solid was dissolved in 40 ml. of 2% sodium hydroxide. The solution was clarified by filtration and acidified to *p*H 2 with concentrated hydrochloric acid. The precipitated product (207 mg.) was collected and dried, m.p. 210-256°. Recrystallization from 20 ml. of 95% ethanol afforded the analytical sample, 157 mg. (61%), m.p. 242-258°; ir (Nujol) μ 3.8 (broad, acid OH), 5.9 (broad, C=O). A sample again recrystallized melted at 258-262° but was unchanged in the infrared.

Anal. Calcd. for $C_{15}H_{12}O_2S$: C, 70.3; H, 4.73; S, 12.5. Found: C, 70.1; H, 4.81; S, 12.7.

Methyl 1,4-Dimethyl-2-dibenzothiophenecarboxylate (XI).

Method A. From the Acid (X).

A suspension of 475 mg. (1.85 mmoles) of X in 60 ml. of saturated anhydrous methanolic hydrogen chloride was refluxed for 5 hours. The resultant solution was concentrated, the residual solid was dissolved in dichloromethane, and any free acid was removed by washing with sodium hydroxide. Concentration to remove the dichloromethane afforded 464 mg., m.p. 69-84°, of ester. Methanol recrystallization yielded 339 mg. (68%), m.p. 86-87.5°; uv (ethanol), λ max mμ 243 (ϵ, 53,700), 259(ϵ, 34,200), 316 (ϵ, 2,690), 329 (ϵ, 3,390); ir (Nujol) μ 5.84 (ester C=O); nmr (deuteriochloroform) δ 8.45-8.20 m (aryl H-9), 7.90-7.65 m (aryl H-6), 7.57 s (aryl H-3), 7.52-7.25 m (2 aryl H's), 3.92 s ($COOCH_3$), 2.98 s (1-CH_3), 2.45 s (4-CH_3).

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.1; H, 5.23; S, 11.9. Found: C, 71.2; H, 5.23; S, 12.1.

Method B. From the Tetrahydro Ester (XXI) (see below).

A mixture of XXI (60 mg., 0.22 mmole) and 60 mg. of 30% palladium-carbon was heated at 240-250° for 20 hours. The product was recovered from the catalyst by trituration with three 5 ml. portions of dichloromethane, and filtration. Concentration afforded 24 mg. (40%) which partly crystallized. Thin-layer chromatography (R_f 0.7 in benzene on silica gel, spots detected under ultraviolet light) showed two faint contaminants (R_f 0.0-0.1 and R_f 0.9). Isolation of the product from one preparative plate (20 x 20 cm., 1 mm. layer of silica gel, in benzene; XI was eluted from the center band with dichloromethane) afforded 9.6 mg. which crystallized, m.p. 82-84°, identical in ir and nmr spectra with XI from Method A; uv extinctions indicated the purity was 96%. Mixture melting point with XI from Method A was 83-86°.

4′-Chloromethyl-2′,5′-acetoxylidide (XIII).

An ice-cold suspension of 3.00 g. (18.3 mmoles) of 2′,5′-acetoxylidide in 30 ml. of dichloromethane containing 2.20 g. (27.3 mmoles) of chloromethyl methyl ether was treated with a solution of 2.5 ml. of anhydrous stannic chloride in 15 ml. of dichloromethane. The resultant solution was stirred at 25° for 1 hour and poured into 100 ml. of ice and water. The white precipitate was collected, washed with water and dried (2.94 g.). Additional product (0.56 g.) was recovered from the filtrate by separating the organic layer, extracting the water layer with 50 ml. more of dichloromethane, washing the combined extracts with water, drying the extract, and evaporation. The combined product was triturated with 80 ml. of boiling ethyl acetate; the insolubles were collected on a filter and treated again with 50 ml. of hot ethyl acetate. The ethyl acetate filtrates were combined and concentrated to incipient crystallization. After 4 hours at 5°, 2.3 g. (60%) was collected, m.p. 182-184°. An analytical sample from another run melted at 181-182°; uv (ethanol) λ max mμ 243 (8500); ir (Nujol) μ 3.06 (NH), 6.02 (C=O), 6.52 (amide II).

Anal. Calcd. for $C_{11}H_{14}ClNO$: C, 62.4; H, 6.67; Cl, 16.8; N, 6.62. Found: C, 62.4; H, 6.40; Cl, 16.5; N, 6.52.

4′-Formyl-2′,5′-acetoxylidide (XIV).

To a solution of 0.57 g. (11 mmoles) of sodium methoxide in 11 ml. of absolute ethanol was added, with ice-cooling and stirring, 1.05 ml. of 2-nitropropane (practical) in portions; after a few minutes, 2.2 g. (10 mmoles) of the chloromethyl compound (XIII) was added, and the ice bath was removed. After 15 minutes' stirring, the temperature rose to 55°. After 3.5 hours, the mixture was poured into 50 ml. of water, stirring was continued for 1 hour, and the white solid was collected on a filter, washed with water, and dried, yielding 1.89 g. (95%), m.p. 148-158°. The infrared spectrum was unchanged after recrystallization of a 1.50 g. sample from 25 ml. of ethyl acetate to give 1.04 g. (52%), m.p. 156-159°; ir (Nujol) μ 3.05 (NH), 5.90 (aldehyde C=O), 6.01 (amide C=O); nmr (deuteriochloroform) δ 10.17 s (–CH=O), 7.88 s (aryl H-3′), 7.57 s (aryl H-6′), 2.60 s (5′-CH_3), 2.27 s (2′-CH_3), 2.23 (CH_3CO–N).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.85; N, 7.33. Found: C, 69.1; H, 6.82; N, 7.46.

4-Acetamido-2,5-dimethylbenzoic Acid (XV).

A suspension of silver oxide was freshly prepared from 533 mg. (3.15 mmoles) of silver nitrate in 2 ml. of water and 250 mg. (6.30 mmoles) of sodium hydroxide in 2 ml. of water. To it was added a solution of 286 mg. (1.50 mmoles) of the acetamido aldehyde XIV in 12 ml. of 95% ethanol, and the mixture was stirred for 45 minutes and filtered. The filtrate (and water washes) was acidified to *p*H 2 with concentrated hydrochloric acid. A white precipitate formed on standing; collected, washed with water, and dried, it weighed 150 mg. (48%), m.p. 257-259°. The combined water wash and acid filtrate were extracted with ethyl acetate and with methylene chloride to yield additional crude product, 128 mg., which was recrystallized from 7 ml. of 95% ethanol giving 119 mg., m.p. 256-257.5° (86%); ir (Nujol) μ 3.08 (NH), 3.7-4.0 (acid OH), 5.95 (acid (C=O), 6.0 (shoulder, amide C=O).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.32; N, 6.76. Found: C, 63.7; H, 6.31; N, 6.89.

4-Amino-2,5-dimethylbenzoic Acid (XVI).

A suspension of 6.87 g. (36.0 mmoles) of acetamido aldehyde XIV and 14.3 g. (84.2 mmoles) of silver nitrate in 180 ml. of refluxing water was treated dropwise, during 30 minutes, with a solution of 16.5 g. (0.41 mole) of sodium hydroxide in 100 ml. of water. Black silver oxide precipitated; within about 30 minutes the white suspension of XIV had disappeared and a silver mirror appeared on the walls of the flask. To ensure complete deacetylation, the mixture was refluxed overnight, then filtered. Acidification of the filtrate with concentrated hydrochloric acid to *p*H 3.5-4.0 precipitated an orange solid, which was collected, washed with water, and dried, weighing 4.29 g. (72%), m.p. 178-186°. Recrystallization from 95% ethanol yielded 2.1 g. (35%). m.p. 188-190°; ir (Nujol) μ 2.86 and 2.94 (NH), 3.75-4.0 (acid OH), 6.0 (acid C=O), 6.15 (NH_2, aryl).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.4; H, 6.71; N, 8.48. Found: C, 65.3; H, 6.75; N, 8.27.

Methyl 4-Amino-2,5-dimethylbenzoate (XVII).

A solution of 1.65 g. (10.00 mmoles) of the amino acid XVI in 50 ml. of saturated anhydrous methanolic hydrogen chloride was refluxed overnight, and concentrated. A solution of the residual solid in 25 ml. of water was clarified by filtration and basified to *p*H 9 with concentrated ammonium hydroxide. The precipitate, collected on a filter and washed with water, weighed 1.79 g. (100%), m.p. 70-72°. Recrystallization from 10 ml. benzene by adding 14 ml. of petroleum ether (b.p. 30-60°) afforded 0.88 g. (49%), m.p. 72.5-73.5° (lit. m.p. 78-80°) (18); ir (Nujol) μ 2.95, 3.02, 3.12 (NH), 5.88 (ester C=O), 6.10 (NH_2, aryl), 6.41 (N-aryl); nmr (deuteriochloroform) δ 7.70 s (aryl 6-H), 6.43 s (aryl 3-H), 3.99 s (NH_2), 3.83 s ($COOCH_3$), 2.52 s (2-CH_3), 2.12 s (5-CH_3). A sample from a previous run was analyzed without recrystallization, m.p. 52-56.5° (94% yield), identical in nmr spectrum to the above.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.31; N, 7.82. Found: C, 66.9; H, 7.30; N, 7.91.

4-Mercapto-2,5-dimethylbenzoic Acid (XVIII).

The detailed procedure (19) for 4-mercaptobenzoic acid was used. 4-Amino-2,5-dimethylbenzoic acid (XVI) (3.3 g., 20 mmoles) was diazotized in hydrochloric acid with sodium nitrite and added to a freshly prepared sodium polysulfide solution. After reaction, accompanied by much foaming, was complete, acidification afforded 3.6 g. (100%), m.p. 250-282°, of the disulfide of XVIII. The infrared spectrum was identical to a sample for analysis which had been recrystallized from 1,2-dimethoxyethane-2-propanol-water (3:1:2), m.p. 295-300°.

Anal. Calcd. for $C_{18}H_{18}O_4S_2$: C, 59.6; H, 5.00; S, 17.7. Found: C, 59.5; H, 5.11; S, 17.0.

Zinc-acetic acid reduction ot 1.70 g. (4.7 mmoles) of the disulfide afforded 1.44 g. of crude product XVIII, m.p. 158-162°. Recrystallization from 18 ml. of ethanol-water (2:1) yielded 1.04 g. (55% based on XVI), m.p. 161-164°; ir (Nujol) μ 3.7-4.0 (acid OH; SH assumed to be obscured in this region), 5.9 (C=O)--absence of a band at 10.4 μ distinguished the spectrum from that of the disulfide; nmr (deuteriochloroform) δ 11.6 s (broad, OH), 7.84 s (aryl H-6), 7.12 s (aryl H-3), 3.43 s (SH), 2.57 s (2-CH_3), 2.31 s (5-CH_3); nmr (deuteriomethanol), δ 7.24 s (H-6), 6.72 s (H-3), 4.42 s (sh), 2.03 s and 1.81 s (aryl CH_3's).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.3; H, 5.53; S, 17.6. Found: C, 59.0; H, 5.43; S, 17.3.

4-(2-Ketocyclohexylthio)-2,5-dimethylbenzoic Acid (XIX).

To a partial solution of the mercapto acid XVIII (1.08 g., 5.93 mmoles) in 11 ml. of water containing 0.673 g. (12.0 mmoles) of potassium hydroxide was added 0.796 g. (6.00 mmoles) of 2-chlorocyclohexanone. The mixture was stirred at 5° for 1 hour, then heated on a steam bath. Additional base was added to maintain a *p*H of 8-9, followed by 0.65 g. more 2-chlorocyclohexanone. After 2 hours, during which some of the potassium salt of XIX precipitated, the mixture was filtered. Acidification of the filtrate with concentrated hydrochloric acid to *p*H 2 precipitated 0.91 g. of XIX, m.p. 155-182°. An additional 0.68 g. was obtained from the potassium salt on the filter by acidification to *p*H 2 of a stirred aqueous suspension. The combined product was recrystallized from 30 ml. of methanol-water (5:1), and yielded 1.06 g. (64%), m.p. 183-188°; ir (Nujol) μ 3.8-4.0 (acid OH), 5.85 (ketone C=O), 5.97 (acid C=O).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.7; H, 6.50; S, 11.5. Found: C, 64.4; H, 6.75; S, 11.5.

Methyl 4-(2-Ketocyclohexylthio)-2,5-dimethylbenzoate (XX).

Esterification of the ketone acid (XIX) and purification of XX (86% yield) was as described for compound XI. Recrystallization from hexane (7 ml./g.) yielded 37% of XX, m.p. 88-90°; ir (Nujol) 5.82 (C=O, ester and ketone); nmr (deuteriochloroform) δ 7.73 s (aryl H-6), 7.20 s (aryl H-3), 4.0 s (broad, CO–CH–S), 3.87 s ($COOCH_3$), 3.3-1.7 (cyclohexyl, 4 CH_2's), 2.55 s (2-CH_3), 2.38 s (5-CH_3).

Anal. Calcd. for $C_{16}H_{20}O_3S$: C, 65.7; H, 6.88; S, 10.9. Found: C, 66.0; H, 6.85; S, 11.0.

Methyl 6,7,8,9-Tetrahydro-1,4-dimethyl-2-dibenzothiophenecarboxylate (XXI).

The ketone ester (XX) (219 mg., 0.747 mmole) and 4.6 g. of polyphosphoric acid (82-84% phosphorus pentoxide) were thoroughly mixed by stirring, then heated at 40-45° for 4 hours. The dark brown mixture was hydrolyzed by stirring, in portions, with 30 g. of ice. The product separated as a pale precipitate, and was extracted with three 25-ml. portions of ether. The ether extract was washed with 40 ml. of 5% sodium hydroxide, with two 40-ml. portions of water, dried, and concentrated. The residual syrup, 177 mg. (86%), according to thin-layer chromatography with benzene on silica gel (spots detected with ultraviolet light), was free of XX (R_f 0.2) but contained two contaminants (R_f 0.0, heavy; and R_f 0.4, faint) in addition to the product (XXI) (R_f 0.7). (That the main contaminant was probably from polymerization of the tetrahydro ring was suggested in the nmr spectrum by extraneous signals for H-3, carbomethoxy and aryl methyl. The product was isolated from two chromatographic plates (20 x 20 cm., 2-mm. layer of silica gel, in benzene) to yield 65 mg. (32%), m.p. 80-83°; nmr (deuteriochloroform) δ 7.42 s (aryl H-3), 3.92 s ($COOCH_3$), 3.3-2.7 m (benzylic CH_2's at C.6 and C.9), 2.86 s (9-CH_3), 2.45 s (6-CH_3), 2.0-1.75 m (CH_2's at C.7 and C.8).

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